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Radiotherapy of NPC

Recommendation for a contouring method and atlas of organs at risk in nasopharyngeal carcinoma patients receiving intensity-modulated radiotherapy

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ABSTRACT

Background and purpose: To recommend contouring methods and atlas of organs at risk (OARs) for nasopharyngeal carcinoma (NPC) patients receiving intensity-modulated radiotherapy, in order to help reach a consensus on interpretations of OARs delineation.

Methods and materials: Two to four contouring methods for the middle ear, inner ear, temporal lobe, parotid gland and spinal cord were identified via systematic literature review; their volumes and dosimetric parameters were compared in 41 patients. Areas under the receiver operating characteristic curves for temporal lobe contouring were compared in 21 patients with unilateral temporal lobe necrosis (TLN).

Results: Various contouring methods for the temporal lobe, middle ear, inner ear, parotid gland and spinal cord lead to different volumes and dosimetric parameters ($P < 0.05$). For TLN, D1 of PRV was the most relevant dosimetric parameter and 64 Gy was the critical point. We suggest contouring for the temporal lobe, middle ear, inner ear, parotid gland and spinal cord. A CT–MRI fusion atlas comprising 33 OARs was developed.

Conclusions: Different dosimetric parameters may hinder the dosimetric research. The present recommendation and atlas, may help reach a consensus on subjective interpretation of OARs delineation to reduce inter-institutional differences in NPC patients.

Radiotherapy is the preferred therapeutic modality for non-metastatic nasopharyngeal carcinoma (NPC). Intensity modulated radiotherapy (IMRT) is currently the mainstay of radiation oncology. Accurate delineation and precise dosage of the target volume and organs at risk (OARs) are the keys to successful radiotherapy.

Many normal tissues close to the nasopharynx are defined as OARs, including the temporal lobe, brainstem, spinal cord, optic nerve, chiasm, parotid gland, submandibular gland, pituitary et al.; therefore, treatment planning is difficult in NPC. Furthermore, critical normal tissues such as the brainstem and temporal lobe are so close to the target volume that inaccurate delineation will mislead treatment planning, resulting in inadequate target volume coverage or OAR overdose. Thus, accurate and consistent OARs delineation in NPC is critical. However, large variations were observed when contouring OARs [1–3]. Furthermore, significantly different contouring methods are also recommended in the literature. For example, when contouring the inner ear, some clinicians delineate the cochlea alone, the internal auditory canal (IAC) in combination with the vestibule and cochlea, the IAC and cochlea, or the vestibule and cochlea [4–7]. Such diversity in OAR contouring will certainly generate unmatched dosimetric parameters, and prevents side effect correlation studies. Thus, guidelines for OARs delineation are necessary. The considerable variation in OARs delineation mainly originates from the diversity of subjective interpretations and variation in actual contouring. In

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this study, we mainly focused on the various subjective interpretations.

We identified different OARs contouring methods and applied these methods in 41 NPC patients, to compare the volumes and dosimetric parameters. Furthermore, as an example, we retrospectively compared the areas under the receiver operating characteristic (ROC) curves for two temporal lobe contouring methods in 21 NPC patients with unilateral temporal lobe necrosis (TLN) who underwent IMRT. A more reasonable contouring method for temporal lobe was obtained. Finally, we recommend a contouring method and atlas of the OARs in NPC patients, for which we expect to reach a consensus on interpretations of OARs delineation.

Methods and materials

Delineation methods

A review of the literature regarding OARs delineation in head and neck cancer (HNC) revealed two to four contouring methods for the middle ear, inner ear, temporal lobe, parotid gland and spinal cord. Information for this review was identified by searches of PubMed using the name of the organs (such as temporal lobe, et al.) and search terms "contouring", "delineation" or specific radiation injuries (such as temporal lobe necrosis, temporal lobe injury, et al.) and "radiation therapy"/"radiotherapy" in the title/abstract (or radiation injury and "radiation therapy"/"radiotherapy" in title for the spinal cord and parotid gland). References were supplemented with relevant citations from the reference lists of the retrieved papers. Relevant papers were defined as clinical studies or reviews elaborating on the organs contouring or presenting pictures of delineated OARs on sectional CT or MRI. Papers published until the end of November 2012 were included. All papers identified in the searches were selected on the basis of the above criteria by the first author (Sun Y.) after reading the abstract. Totally, 97, 146, 178, 94 and 38 papers were identified and 5, 30, 13, 7 and 7 papers were found to be relevant for the temporal lobe, parotid gland, spinal cord, inner ear and middle ear, respectively (Supplementary References 1). For the other OARs, different contouring methods were few referred [8–10].

Two methods were used to contour the temporal lobe. The first included brain tissue outside the Sylvian fissure and basal ganglia, excluding the parahippocampal gyrus and hippocampus (method 1); the other method contoured the temporal lobe including the parahippocampal gyrus and hippocampus, excluding the basal ganglia and insula (method 2) [11]. Three middle ear contouring methods were identified: contouring the combination of tympanum and Eustachian tube (ET) [5]; the tympanum and bony part of the ET respectively, [12]; or the ET, tympanic cavity and mastoid process, respectively [13]. As described above, four methods were observed for inner ear [4–7]. Spinal cord contouring included the true spinal cord [14], or the bony limits of the spinal canal [15]. Chau et al. split the parotid gland into the gross tumor volume-overlapping, planning target volume-overlapping and non-target-overlapping sub-segments [16]. As no parotid gland involvement was detected in this study, we delineated the complete parotid gland and non-target-overlapping sub-segments. By reviewing atlases of anatomy [8–10], we defined 3D-boundaries for other OARs, and suggested representative contouring according to their anatomic locations on CT–MRI fusion.

Application of different contouring methods

A total of 41 consecutive, newly diagnosed, non-metastatic NPC patients were treated in our hospital between March 2011 and September 2011. The patients' characteristics are presented in Supplementary Table 1.

According to International Commission on Radiation Units and Measurements (ICRU) reports 50, 62 and 83, we contoured the gross target volume (GTV), clinical target volume (CTV) and OARs using the delineation methods described above. Atlas-based auto segmentation (ABAS, Version 2.01, ELEKTA CMS, INC., Stockholm, Sweden) was used to generate primary OARs delineation. Then, the contouring was modified and completed by Sun Y. who specializes in HNC with 11 years work experience, and then was reviewed by a radiologist (Zhang R.) with more than 20 years work experience. The differences were resolved by group discussion. A 3 mm margin was used to generate the corresponding planning target volume and planning organs at risk volume (PTV/PRV). A total dose of 70 Gy at 2.12 Gy per fraction (5 fractions per week) was prescribed. According to the Radiation Therapy Oncology Group (RTOG) protocols 0225 and 0615 and ICRU report 83, we calculated the volume of all organs; the mean dose (Dmean) for the parotid gland, middle and inner ear, D1 of PRV (Dx/xcc, the minimum dose received by the "hottest" x% or x ml of the structure) for the spinal cord and temporal lobe to compare the different contouring methods.

Selection of temporal lobe contouring methods

We retrospectively analyzed the dosimetric parameters in 21 NPC patients with unilateral TLN who underwent IMRT between November 2004 and November 2006. The patients' characteristics are presented in Supplementary Table 1.

The median follow-up time was 45 months (range: 38–63 months) and the latency of TLN was 35 months (range: 25–57 months) after completion of radiotherapy. The patients underwent follow-up (clinical and/or imaging examinations) monthly in the first three months after completion of radiotherapy, every three months in the first three years, every six months in the next two years, and annually thereafter. MRI was required every six months during the first 2 years and annually thereafter, and was also performed when tumor recurrence or TLN was suspected [17]. MRI findings were independently reviewed by two radiologists, and any disagreements were resolved by consensus. A diagnosis of TLN will be made if the MRI presented following signs, (1) WMLs (homogeneous lesions in the white matter); (2) solid, enhanced nodules with or without a necrotic center and finger signs; (3) cysts of round or oval lesions [18–19]. Tumor recurrence or metastasis of tumor was excluded.

Statistical analysis

SPSS 16.0 was used for data analysis. We performed the Friedman test to compare middle/inner ear Dmean; the paired-*t* test to compare parotid gland volume and Dmean, spinal cord volume and D1 of PRV; the Wilcoxon-test to compare temporal lobe the volume, and D1 of PRV for the 41 patients.

For the 21 patients with unilateral TLN, three steps were adopted. Firstly, the paired-*t* test was used to compare all the dosimetric parameters (the D1–D60, D1–D40 cc, V10 [Vx, the percentage volume of the organ which received more than × Gy] to V75, D1–D60 of PRV, and V20–V75 of the PRV at five units intervals) between the temporal lobes with and without radiation-induced damage for every method. All of the significantly different parameters from the paired *t*-tests were separately included in the next analyses. Secondly, multivariate analysis using the binary logistic regression model was used to identify the most relevant parameters associated with TLN. Lastly, the areas under the ROC curves of the most relevant parameters from the two contouring methods were compared to select a more reasonable contouring method. $P < 0.05$ was considered significant.

Results

Comparison of dosimetric parameters in the OARs using different contouring methods

Significant differences in the volume and selected parameters of all organs were observed using different contouring methods ($P < 0.05$; Table 1).

Significant differences between the ipsilateral and contralateral temporal lobe were observed for all dosimetric parameters ($P < 0.05$, Supplementary Table 2). The D1 of PRV was identified as the most relevant parameter for TLN for both methods (Table 2). The method 2 has a slightly larger area under the ROC curve than method 1 (0.86 vs. 0.85); 64 Gy was the critical point for the D1 of PRV (Supplementary Fig. 1). There was no significant difference between the areas under the ROC curves of the two contouring methods ($P = 0.27$).

Recommendation for OARs contouring

Based on the anatomic definition and pathogenesis of radiation-induced injury, we recommend a reasonable contouring method for temporal lobe, middle ear, inner ear, parotid gland and spinal cord (Table 3). For other organs whose contouring is rarely described, we recommend outlining the whole organ according to their anatomic definition [8–10,22–24] (Supplementary Table 3). The middle ear, inner ear and TMJ should be delineated on the bone window (1400–1600/400–600 HU or 3000–4500/600–800 HU) [5,25], the temporal lobe and brainstem on the brain windows (80–100/35–50 HU); however, the lateral boundary of the temporal lobe and other organs should be delineated on the soft tissue window (300–400/20–120 HU, Fig. 1) [25]. The complete OARs contouring atlas is presented in Supplementary Fig. 2.

Table 2
Multivariate analysis of the two temporal lobe contouring methods in 21 NPC patients with TLN.

	B[a]	S.E.	Wald[b]	*P*-value
Method 1[c]				
D1 of PRV[d]	2.69	1.36	3.91	0.05
D40cc[e]	-0.48	0.18	6.82	0.009
D0.5 cc[e]	-1.84	1.10	2.780	0.095
Method 2[f]				
D1 of PRV[d]	0.57	0.18	10.53	0.006
V10[g]	-0.2	0.07	7.61	0.001

Abbreviations: S.E., standard error; PRV, planning organ at risk volume.
[a] β, meaning the regression coefficient.
[b] Wald, the nonzero test of the regression coefficients.
[c] Temporal lobe including the basal ganglia and insula, excluding parahippocampal gyrus and hippocampus.
[d] D1 of PRV is the minimum dose received by the "hottest" 1% of the temporal lobe PRV.
[e] $D_{0.5cc}$ is the minimum dose received by the "hottest" 0.5 ml of the temporal lobe volume; D_{40cc} is the minimum dose received by "hottest" 40 ml of the temporal lobe volume.
[f] Temporal lobe including parahippocampal gyrus and hippocampus, excluding basal ganglia and insula.
[g] V10 is the volume percentage of the temporal lobe that received more than 10 Gy.

We suggest the temporal lobe includes the hippocampus, parahippocampal gyrus and uncus; the basal ganglia and insula are located anteriorly and superiorly to the hippocampus and parahippocampal gyrus should be excluded. Gondi et al. further elaborated on the location of the hippocampus on MRI [26]. We suggest contouring the tympanic cavity and bony part of the ET individually. The tympanic cavity is delineated laterally by the tympanic membrane, defined by the ligature between the two

Table 1
Comparison of dosimetric parameters for the OARs using different contouring methods in NPC patients receiving IMRT.

Organs	Volume (ml)	*P*-value	Dmean (Gy)[i]	*P*-value
Middle ear				
Middle ear[a]	19.4 ± 1.0	<0.001	35.4 ± 0.6	<0.001
Tympanic cavity	0.7 ± 0.2		49.1 ± 0.9	
ET	0.2 ± 0.02		60.0 ± 0.8	
Tympanic cavity + ET[b]	0.5 ± 0.1		51.5 ± 0.9	
Mastoid process	16.8 ± 0.9		34.6 ± 0.6	
Inner ear				
Inner ear[c]	2.9 ± 0.1	<0.001	46.0 ± 0.8	<0.001
Cochlea	0.2 ± 0.004		52.1 ± 0.9	
Vestibule	0.3 ± 0.01		41.7 ± 0.9	
Vestibule + cochlea[d]	0.5 ± 0.1		45.9 ± 0.8	
IAC	0.3 ± 0.2		49.4 ± 0.9	
Parotid gland				
Complete parotid	28.9 ± 1.0	<0.001	40.5 ± 5.9	<0.001
Spared parotid[e]	24.1 ± 1.0		34.4 ± 5.8	
	Volume (ml)	*P*-value	D1 of PRV (Gy)[i]	*P*-value
Spinal cord				
True spinal cord	22.4 ± 2.1	<0.001	44.7 ± 0.9	0.001
Vertebra canal[f]	36.5 ± 5.2		48.1 ± 1.6	
Temporal Lobe				
Method 1[g]	94.9 ± 1.3	<0.001	64.0 ± 0.7	0.003
Method 2[h]	102.7 ± 1.4		63.4 ± 0.6	

Abbreviations: OAR, organ at risk; ET, Eustachian tube; IAC, internal auditory canal; PRV, planning organ at risk volume.
[a] Whole middle ear including tympanic cavity, bony part of ET and mastoid process.
[b] Combination of tympanum and bony part of ET.
[c] Whole inner ear including the cochlea, vestibule and IAC.
[d] Combination of vestibule and cochlea.
[e] Non-target-overlapping sub-segment.
[f] Outlined according to the bony limits of the spinal canal.
[g] Temporal lobe excluding parahippocampal gyrus and hippocampus, including the basal ganglia and insula.
[h] Temporal lobe including parahippocampal gyrus and hippocampus, excluding the basal ganglia and insula.
[i] Dx, the minimum dose received by the "hottest" x% of the organ; Dmean, mean dose received by organ.

Table 3
Anatomic boundaries of the temporal lobe, parotid gland, spinal cord, middle ear and inner ear in NPC.

Organ	Standard TPS name [20]	Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Temporal lobe	TemporalLobe[a]	Cranial edge of the sylvian fissure	Base of middle cranial fossa	Temporal bone and sylvian fissure, greater wing of sphenoid	Petrous part of temporal lobe, tentorium of cerebellum, incisura preoccipitalis	Temporal bone	Cavernous sinus, sphenoid sinus, sella turcica, and sylvian fissure including parahippocampal gyrus and hippocampus
Parotid gland [21]	Parotid[a]	External auditory canal, mastoid process	Appearance post. part submandibular space	Masseter m. post. border mandibular bone, medial pterygoid m.	Ant. belly sternocleidomastoid m., lat. side post. belly of the digastric m. (posterior medial), mastoid process	Submandibular fat, platysma	Post. belly of the digastric m., styloid process, parapharyngeal space, sternocleidomastoid
Spinal cord	SpinalCord	Disappearance of cerebellum	Two centimeters below the inferior edge of the clavicular head	Exclude the subarachnoid space			
Inner ear	Ear_Inner[a]	Cochlea and internal auditory canal should be individually delineated and named					
Middle ear	Ear_Middle[a]	Tympanic cavity, bony part of Eustachian tube should be individually delineated and named					

[a] The organs should be divided into left and right, and the standard TPS name of laterality is indicated by appending an underscore character (_), followed by L or R, respectively. For example, the left parotid is named Parotid_L; the right parotid is named Parotid_R.

bony structures with an increased density along the anterior and posterior walls of the most medial aspect of the outer air canal [5], the sharp narrow region connected interiorly to the ET, and the interface between the temporal bone and air at all other walls. For the inner ear, we suggest delineation of the cochlea and IAC individually. The cochlea is located anteriorly to the IAC [5]. The visible true spinal cord should be contoured from the foramen magnum (the level of the odontoid process of the axis) to 2 cm below the inferior edge of the head of the collarbone. The whole parotid gland should be outlined, including the external carotid artery [11] and the region within CTV, but not the GTV. Water et al. elaborate further on definitive bordering of the parotid gland [23].

Discussion

Accurate and consistent OARs delineation is critical for IMRT. However, considerable heterogeneity contouring has been observed in OARs contouring [1–3]. Nelms et al. found the most variable contour in HNC occurred in the brainstem, parotid glands and spinal cord, with mean consistency scores less than 70/100 [1]. Such contouring variations originated from both the subjective diversity of OARs interpretation and variation in actual contouring. In this study, we mainly focused on subjective OARs interpretation which varies significantly through a literature review. Various contouring methods will lead to different dosimetric parameters, and prevents dosimetry/side effect correlation studies. Thus, a uniform contouring is necessary to minimize contouring variations.

For the 21 NPC patients with unilateral TLN, paired *t*-test was first used to exclude the irrelevant parameters with TLN. The multivariate analysis using the binary logistic regression model was used to identify the most relevant parameters. Lastly, the most relevant parameters from the two methods were analyzed using the ROC curve, which has been used in NPC to select a prognostic factor and the critical point [27–28]. In this study, the value of D1 of PRV can better reflect the development of TLN if one method has a bigger area under the ROC curve than the other one. The critical point was defined by achieving a minimum of 80% sensitivity and within this constraint maximized the sensitivity and specificity with the maximum Youden score [27–29].

In this study, we demonstrated that various contouring methods will lead to different dosimetric parameters, in contrast to Feng et al. who reported that treatment planning optimization was not substantially affected by different OAR contours [2]. This discrepancy can be explained as follows: Firstly, we evaluated the different contouring methods with a large subjective diversity of OARs interpretation, rather than the reproducibility of the same interpretation. Secondly, Feng et al. evaluated the doses received by the organs which are relatively far away from the target volume. However, in our study, the temporal lobe, inner ear, etc. are closer to the nasopharyngeal target volume, often lie on steep dose gradients; therefore, the dose of these OARs may be impacted more significantly by contouring uncertainties.

Radiation-induced temporal lobe injury is characterized by TLN, observed in 1–56% of NPC patients after radiotherapy [30,31]. Our study retrospectively compared the areas under the ROC curves for two different temporal lobe contouring methods, found the D1 of PRV was the most relevant dosimetric parameter for TLN, and 64 Gy was the critical dose, similar to the 65 Gy limit recommended by RTOG 0225 protocol. The area under the ROC curves was not significantly different between the two contouring methods. This may be explained as follows: The D1 of PRV is mainly impacted by the inferior and medial aspect of the temporal lobe [17], where TLN is mostly observed [32]. Both methods included the inferior and medial aspect. Thus, no significant difference was observed in the associations of D1 of PRV with the development of TLN.

The biggest controversy in contouring the temporal lobe is whether the hippocampus, parahippocampal gyrus, basal ganglia and insula should be included. We recommend method 2 for the following reasons. Firstly, the hippocampus and parahippocampal gyrus are located close to the target volume, in which the TLN usually occurred (13/21 in this study), while in the basal ganglia and insula rarely occurred (1/21 in this study). Secondly, the symptoms of TLN such as decreased memory, acalculia et al. are correlated with the damage to the hippocampus and parahippocampal gyrus. Finally, method 2 is consistent with the anatomic definition of the temporal lobe.

Radiation-induced middle ear damage is characterized by otitis media with effusion (OME), suffered by 26–40% NPC patients within 5 years after radiotherapy [12,33]. Two factors contributed to OME: (1) damage to the ET, tensor veli palatini muscle, cartilage or nerves; (2) direct radiation damage leading to noninfectious inflammation [13]. Therefore, the injuries of ET and tympanic cavity (including the otosteon) are relevant to the development of OME and should be contoured and protected individually.

Inner ear radiation-induced injury is mainly responsible for sensorineural hearing loss (SNHL), with morbidity rates of 11–57% [4,34]. The precise mechanisms are obscure. Our recommendation to contour the cochlea and IAC individually is based on the inner ear function. During sound transmission, vibration passes from the tympanic membrane to the otosteon, fenestra vestibule and through the cochlea to vibrate the cochlear basilar membrane and produce nerve impulses, which are transported into the

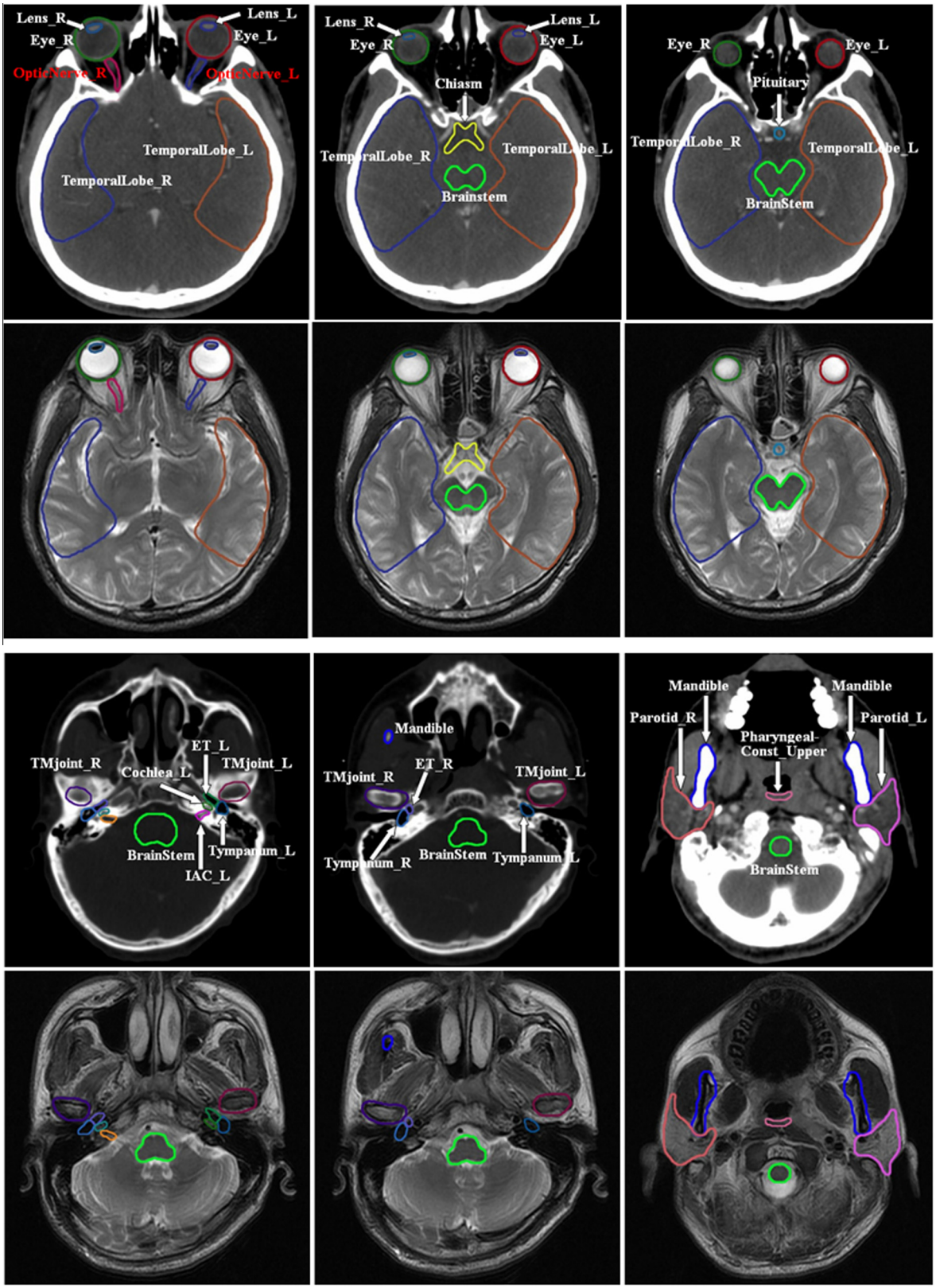

Fig. 1. Brief atlas of OARs in NPC.

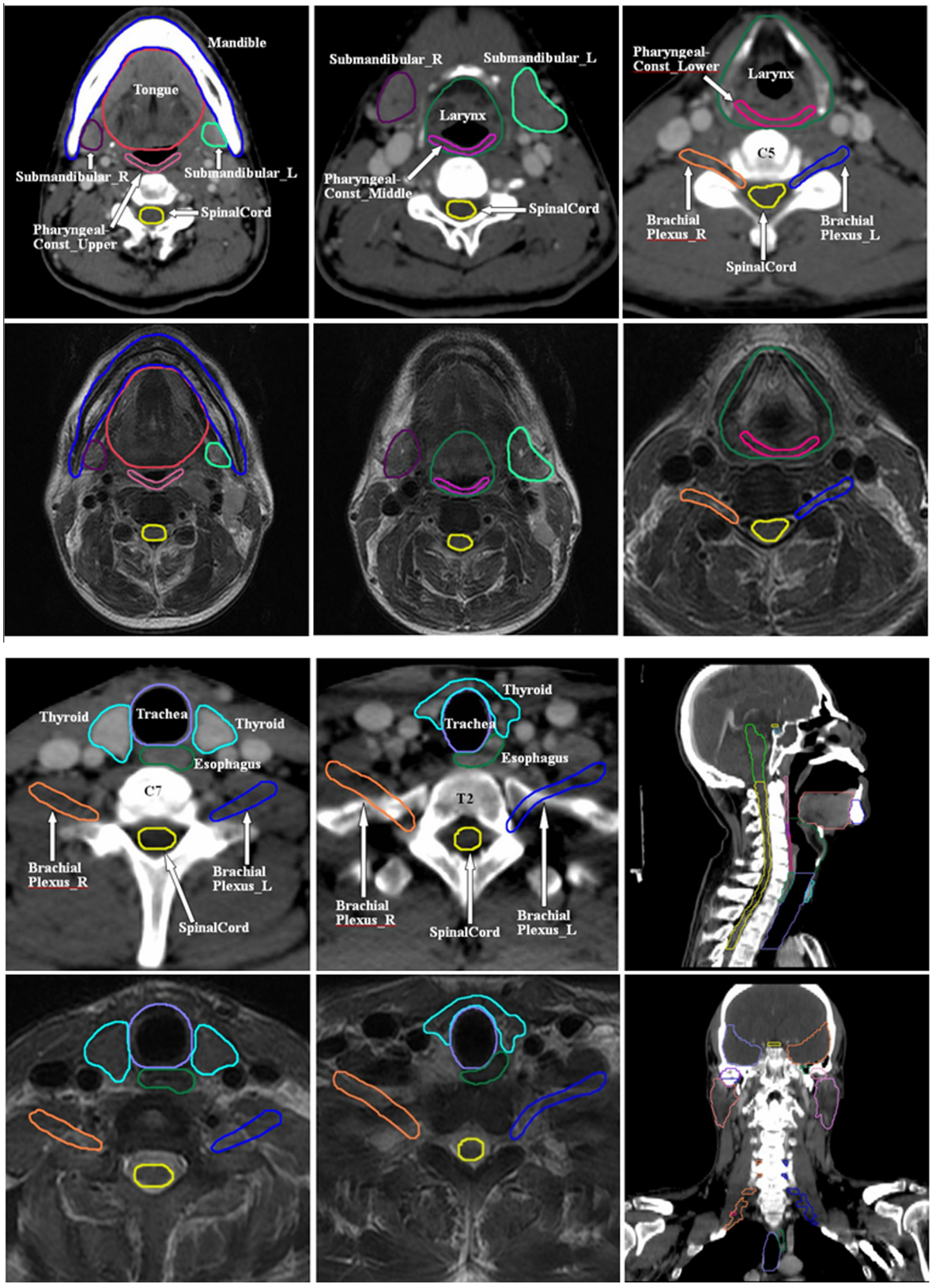

Fig. 1 (*continued*)

auditory center via the cochlear nerve to generate the auditory signal. Dysfunction in any structure of this conduction pathway may lead to SNHL. Thus, the cochlea and cochlear nerve should be contoured and protected individually.

The largest controversy of parotid gland contouring lies in the overlap between the parotid gland and CTV. The parotid gland receives a dose influenced by the size of the target volume and prescribed dose. Radiation-induced xerostomia in NPC patients

can recover years after radiotherapy [35]. Contouring the whole salivary gland minus the GTV may be more suitable for getting the better dosimetric parameters that correspond with the change of salivary function after radiotherapy.

Our recommendation to delineate the true spinal cord is in contrast to Kong et al. [15] for the following reasons: The transverse diameter of the cervical spinal cord is greater than the thoracic spinal cord, and is easier to visualize. In addition, a PRV was generated to ensure that the dose not to exceed the tolerance of spinal cord.

Baxi et al. briefly introduced OARs contouring in nasopharyngeal IMRT [11]. We contoured other organs such as the brainstem, optic nerve et al. according to their 3D anatomical boundaries. The whole organs should be outlined, including those in CTV, but not GTV. According to ICRU report 50, the OARs are defined as critical normal structures. Thus, those overlapping with the GTV, which is considered as part of the tumor, should not be included. On the other hand, OARs within the CTV, lacking of evidence of tumor involvement, should be included. Furthermore, such OARs contouring has also been performed in patients with lung cancer and hepatocellular carcinoma undergoing radiotherapy [15,36]. In this study, we used the temporal lobe as an example to show how to define a reasonable contouring method. Similar steps could be taken for other organs.

The present atlas is mainly based on CT and refers to MRI. It is well recognized that MRI has a better resolution for soft tissue, and is usually used to diagnose the soft tissue disease [37,38]. Thus, glands, muscles and other soft tissues should be contoured by referring to MRI. On the other hand, CT can more reliably indicate bone boundaries and joint structures [39]. Thus, the TMJ, middle/inner ear and mandible, which are mainly defined by bone limit, could be contoured based on CT alone.

Conclusions

Different OARs contouring methods result in different dosimetric parameters. A contouring guideline is necessary to facilitate the generation of uniform and comparable dosimetric parameters. The present atlas, based on anatomic definitions and the pathogenesis of radiation-induced injury, may help reach a consensus on subjective interpretation of the OARs delineation to reduce inter-institutional differences in NPC patients.

Conflict of interest statement

The authors indicate no actual or potential conflicts of interest exist.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2013.10.035.

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